

Application No.: 09/493,795
Amendment Dated 20 January 2004
Reply to Office Action of 18 July 2003

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, including listings, of claims in the application.

Listing of Claims

Claim 1 (currently amended): ~~A substantially pure~~ An isolated α -conotoxin peptide having the generic formula I: Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅-Cys-Cys-Xaa₆-Xaa₇-Xaa₈-Xaa₉-Cys-Xaa₁₀-Xaa₁₁-Xaa₁₂-Cys-Xaa₁₃ (SEQ ID NO1:), wherein Xaa₁ is des-Xaa₁, Ile, Leu or Val; Xaa₂ is des-Xaa₂, Ala or Gly; Xaa₃ is des-Xaa₃, Gly, Trp (D or L), neo-Trp, halo-Trp or any unnatural aromatic amino acid; Xaa₄ is des-Xaa₄, Asp, Phe, Gly, Ala, Glu, γ -carboxy-Glu (Gla) or any unnatural aromatic amino acid; Xaa₅ is Glu, Gla, Asp, Ala, Thr, Ser, Gly, Ile, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any unnatural hydroxy containing amino acid; Xaa₆ is Ser, Thr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa₇ is Asp, Glu, Gla, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa₈ is Ser, Thr, Asn, Ala, Gly, Arg, Lys, ornithine, homoarginine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid, His, halo-His, Pro or hydroxy-Pro; Xaa₉ is Thr, Ser, Ala, Asp, Asn, Pro, hydroxy-Pro, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa₁₀ is Gly, Ser, Thr, ~~Ala~~, Asn, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa₁₁ is Gln, Leu, His, halo-His, Trp (D or L), halo-Trp, neo-Trp, Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys, any unnatural basic amino acid or any unnatural aromatic amino acid; Xaa₁₂ is Asn, His, halo-His, Ile, Leu, Val, Gln,

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Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; Xaa₁₃ is des-Xaa₁₃, Val, Ile, Leu, Arg, ornithine, homoarginine, Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any unnatural basic amino acid; and the C-terminus contains a free carboxyl group or an amide group and

wherein (a) the unnatural aromatic amino acid is selected from the group consisting of nitro-Phe and 4-substituted-Phe wherein the substituent is C₁-C₃ alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO₃H and -NHAc, (b) the unnatural hydroxy containing amino acid is selected from the group consisting of such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr and (c) the unnatural basic amino acid is selected from the group consisting of N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolinyl]-Gly and 2-[3-(2S)pyrrolinyl]-Ala.

Claim 2 (currently amended): ~~A substantially pure~~ An isolated α -conotoxin peptide of generic formula I (SEQ ID NO:1) selected from the group consisting of:

a peptide comprising the amino acid sequence Ala-Cys-Cys-Ser-Asp-Arg-Arg-Cys-Arg-Xaa₃-Arg-Cys (SEQ ID NO:5), wherein Xaa₃ of SEQ ID NO:5 is Trp (Dor L), halo-Trp or neo-Trp and the C-terminus contains a carboxyl or amide group; and

a derivative of the peptide of SEQ ID NO:5 thereof,

wherein said derivative comprises an amino acid substitution of the peptide of SEQ ID NO:5 selected from the group consisting of (a) an Arg residue is substituted with Lys, ornithine, homoarginine, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or an unnatural basic amino acid selected from the group consisting of N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolinyl]-Gly and 2-[3-(2S)pyrrolinyl]-Ala, (b) Xaa₃ is substituted with an unnatural aromatic amino acid selected from the group consisting of nitro-Phe and 4-substituted-Phe wherein the substituent is C₁-C₃ alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO₃H or -NHAc, (c) an Asp residue is substituted with a tetrazolyl

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derivative or Gly or a tetrazolyl derivative of Ala, (d) a Ser residue is substituted with Thr, (e) a Cys residue is substituted with a D-Cys or a homosysteine (D or L), or (f) a pair of Cys residues is replaced pairwise with Ser/(Glu or Asp) or Lys (Glu or Asp) Xaa, is Trp (D or L), halo-Trp or neo-Trp, and the C-terminus contains a carboxyl or amide group.

Claims 3-7 (canceled).

Claim 8 (currently amended): The isolated substantially pure α -conotoxin peptide of claim 1, which is modified to contain an O-glycan, an S-glycan or an N-glycan.

Claim 9 (currently amended): The isolated substantially pure α -conotoxin peptide of claim 2 which is modified to contain an O-glycan, an S-glycan or an N-glycan.

Claims 10-38 (canceled).

Claim 39 (currently amended): ~~A substantially pure~~ An isolated α -conotoxin protein precursor comprising the amino acid sequence Phe Asp Gly Arg Asn Ala Pro Ala Asp Asp Lys Ala Ser Asp Leu Ile Ala Gln Ile Val Arg Arg Ala Cys Cys Ser Asp Arg Arg Cys Arg Trp Arg Cys Gly (SEQ ID NO:236).

Claims 40-41 (canceled).